(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number
WO 01/02375 A1

(51) International Patent Classification[7]: C07D 271/06, 413/04

(21) International Application Number: PCT/US00/17577

(22) International Filing Date: 26 June 2000 (26.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/142,202 1 July 1999 (01.07.1999) US

(71) Applicant *(for all designated States except US)*: **AXYS PHARMACEUTICALS, INC.** [US/US]; 180 Kimball Way, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DENER, Jeffrey, Mark** [US/US]; 1948 Vista Cay, San Mateo, CA 94404-2412 (US). **LY, Cuong, Quoc** [US/US]; Apartment #4, 251 Collins Street, San Francisco, CA 94118 (US).

(74) Agents: **KATHARDEKAR, Vinit, G.** et al.; Axys Pharmaceuticals, Inc., 180 Kimball Way, South San Francisco, CA 94080 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

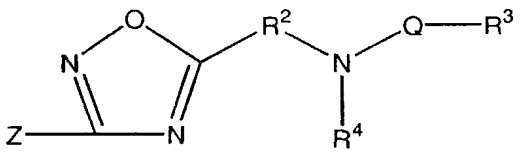
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/02375 A1

(54) Title: PROCESS FOR SYNTHESIZING OXADIAZOLES



(I)

(57) Abstract: The present invention relates to a process for the synthesis of a single as well as large array of oxadiazole based organic compounds. These oxadiazole based organic compounds are represented by compounds of formula (I).

PROCESS FOR SYNTHESIZING OXADIAZOLES

FIELD OF INVENTION

The present invention relates to a process for synthesizing Oxadiazoles.

BACKGROUND OF THE INVENTION

Obtaining a better understanding of the important factors in molecular recognition in conjunction with developing new therapeutic agents has been a major focus of research in the pharmaceutical industry. This process generally begins with screening a large number of compounds against a specific receptor or enzyme. Methods are being developed which permit the synthesis of a large array of compounds, or of mixtures of compounds, that can be screened for their biological activity.

There are however only a few methods that facilitate the quick synthesis of small organic molecules. For this reason, small organic molecules of potential therapeutic interest are still synthesized and evaluated one at a time, thus reducing the number of potential therapeutic agents that could be evaluated for their biological activity.

Oxadiazoles are known to exhibit biological/pharmacological activity. Oxaindoles were first proposed as ester biosteres in conjunction with muscarinic agonist activity by Watjen et al., in J. Med. Chem., 1989, 32, 2281-2291 and Showell et al., in J. Med. Chem., 1991, 34, 1086-1094. Orlek et al., in 1991, J. Med. Chem., 1991, 2726-2735, proposed a benzodiazepine receptor partial activity for Oxadiazoles.

Diana et al., in 1991 reported evaluating oxadiazoles for their antirhinovirus activity (J. Med. Chem., 1994, 37, 2421-2436). Oxadiazoles are thus gaining acceptance and attention as organic molecules having potential therapeutic value. Procedures to synthesize oxadiazoles are known. One such procedure is reported in Synthetic Communications, 12 (6), 457-461 (1992.

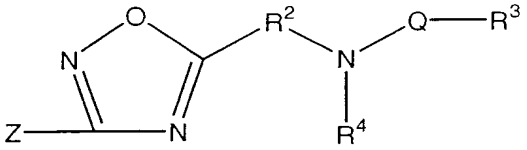
Given the potential therapeutic utility of oxadiazoles, it is important to be able to synthesize oxadiazoles in a rapid fashion. There is thus a need for synthetic methodology which will facilitate synthesis of a single as well as a array of oxadiazole based organic compounds.

SUMMARY OF THE INVENTION

Keeping the above discussed need in mind, the present invention provides a process for the synthesis of a compound or an array of compounds of Formula I. Also provided by the present invention is an array of compounds of Formula I synthesized by the process of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the synthesizing compounds represented by Formula I:



.....Formula I

wherein:

Z represents an aryl group substituted with R^1, R^5 and R^6;

Q represents CO, SO_2 or C(O)NH;

R^2 represents C_1-C_{14} alkylene, C_1-C_{14} substituted alkylene, $(CH_2)_{0-6}$-Ar, Ar-$(CH_2)_{1-6}$, or C_{5-10} cycloalkylene-$(CH_2)_{0-6}$;

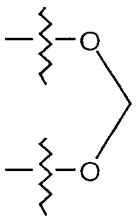
R^3 represents C_1-C_{14} alkyl, aryl, substituted aryl, C_1-C_{14} alkylene-aryl, C_1-C_{10} alkylene-O-aryl, C_1-C_{10} alkylene-S-aryl, heteroaryl or C_1-C_{10} alkylene-S-C_1-C_6 alkyl;

R^4 represents H or C_{1-4} alkyl;

alternatively R^2 and R^4 along with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclic ring substituted with at least one substituent selected from C_{1-4} alkyl, Ph, OH, H, OC_{1-4} alkyl, NHCO-C_{1-4} alkyl and halogen; and

R^1, R^5 and R^6 independently at each occurance are selected from H, C_{1-6} alkyl, O-C_{1-6} alkyl and SO_2-C_{1-4} alkyl;

alternatively, when on adjacent carbon atoms, R^5 and R^6 can be taken together to form



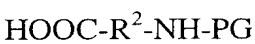
;

said process comprising

(A) treating a compound of Formula 2

.....Formula 2

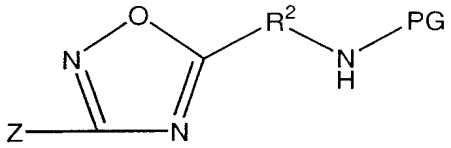
with a compound of Formula 3



.....Formula 3

in the presence of a dehydrating agent and optionally in the presence of a catalyst, at a temperature of from about 25°C to about 85°C,

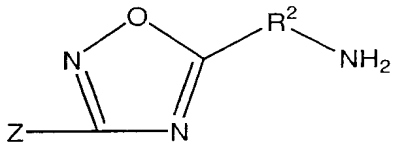
to yield a compound of Formula 4



.....Formula 4

where Z and R^2 are as defined above, and PG represents a protecting group;

(B) treating a compound of Formula 4 with a deprotecting agent, optionally in the presence of a cation scavenger, to yield a compound of Formula 5



.....Formula 5

where Z and R^2 are as defined above;

(C) treating a compound of Formula 5 with:

(i) a compound of Formula 6a

R^3-Q-X .....Formula 6a

in the presence of a base, and where R^3 is as defined above, Q represents CO or SO_2, and X represents a halogen, to form a compound of Formula I, where Q represents CO or SO_2; or

(ii) a compound of Formula 6b

R^3-N=C=O .....Formula 6b

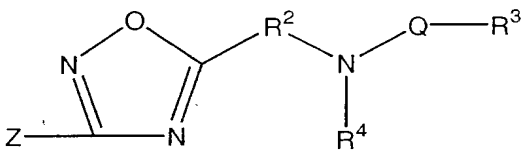
in the presence of a base, and where R^3 is as defined above, to form a compound of Formula I, wherein Q represents C(O)-NH.

A preferred embodiment of the present invention provides a procss wherein the dehydrating agent in step (A) is selected from EDC, DIC, DCC and CDI, and the catalyst in step (A) is selected from DBU, Et_3N, 4-DMAP and HOBt. Another preferred embodiment provides a process wherein the deprotecting agent in step (B) is selected from HCl, HBr, HF, hydrochromic acid, *p*-toluene sulfonic acid, formic acid and TFA.

Yet another preferred embodiment provides a process wherein the cation scavenger in step (B) is anisole and the base in step (C) is selected from N-methyl morpholine, triethyl amine, pyridine, N,N-diisopropyl ethyl amine, N-methyl piperidine, N-ethyl morpholine and 2,6-lutidine. Also provided in yet another preferred embodiment is a process wherein Z represents a phenyl group substituted with R^1, R^5 and R^6; R^1, R^5 and R^6 are independently selected from H, CH_3, C_2H_5, OCH_3, OC_2H_5 and SO_2CH_3; and R^3 represents 2,3,5,6-tetramethyl-phenyl, 3,4-

dimethoxy-phenyl, 2-ethoxy-phen-1-yl, 4-isopropyl-phen-1-yl, 2-Ethoxy-naphthalen-1-yl, 1-phenoxy-propyl-1-yl, phenyl, CH_2-S-Ph, 4-(1,1-Dimethyl-propyl)-phenyl-1-yl, 4-methoxy-benzyl, 2-nitro-benzyl, 4-chloro-phenyl-1-yl, naphthyl, 2-isopropyl-5-methyl-cyclohexyloxymethyl, 4-methoxy-benzyl, 2,3-dichloro-phenyl-1-yl, 1-p-tolyl-cyclopentyl, 6-chloro-pyridin-3-yl, 2,5-dimethyl-phenyl-1-yl, 2-methylsulfanyl-ethyl, 2,6-dichloro-phenyl-1-yl, 1-phenyl-propyl-1-yl, 4-methyl-3-nitro-phenyl-1-yl, 2,3,6-trifluoro-phenyl-1-yl, 3-methyl-butane-1-yl, 4-pentyloxy-phenyl-1-yl, 4-methyl-phenyl-1-yl, 2,4-dimethoxy-phenyl-1-yl, or benzo[1,3]dioxol-5-yl.

Another aspect of the present invention provides an array of compounds of Formula I



.....Formula I

wherein:

Z represents an aryl group substituted with R^1, R^5 and R^6;

Q represents CO, SO_2 or C(O)NH;

R^2 represents C_1-C_{14} alkylene, C_1-C_{14} substituted alkylene, $(CH_2)_{0-6}$-Ar, Ar-$(CH_2)_{0-6}$, or C_{5-10} cycloalkylene-$(CH_2)_{0-6}$;

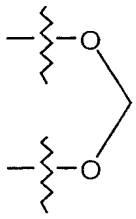
R^3 represents C_1-C_{14} alkyl, aryl, substituted aryl, C_1-C_{14} alkylene-aryl, C_1-C_{10} alkylene-O-aryl, C_1-C_{10} alkylene-S-aryl, heteroaryl, or C_1-C_{10} alkylene-S-C_1-C_6 alkyl;

R^4 represents H or C_{1-4} alkyl;

alternatively R^2 and R^4 along with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclic ring substituted with at least one substituent selected from C_{1-4} alkyl, Ph, OH, H, OC_{1-4} alkyl, NHCO-C_{1-4} alkyl and halogen; and

R^1, R^5 and R^6 independently at each occurance are selected from H, C_{1-6} alkyl, O-C_{1-6} alkyl and SO_2-C_{1-4} alkyl;

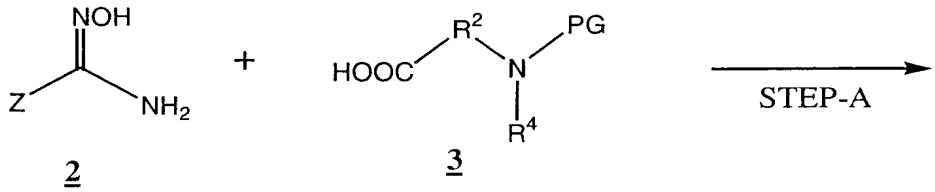
alternatively when on adjacent carbon atoms, R^5 and R^6 can be taken together to form



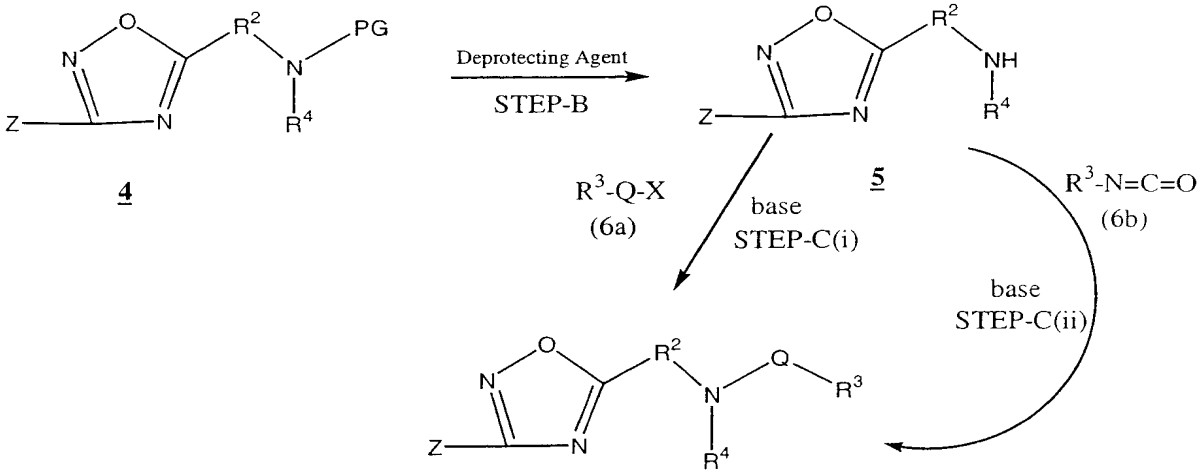
A preferred embodiment of this aspect of the present invention provides an array of compounds wherein, R^1, R^5 and R^6 are independently selected from H, CH_3, C_2H_5, OCH_3, OC_2H_5 and SO_2CH_3; and R^3 represents 2,3,5,6-tetramethyl-phenyl, 3,4-dimethoxy-phenyl, 2-ethoxy-phen-1-yl, 4-isopropyl-phen-1-yl, 2-Ethoxy-naphthalen-1-yl, 1-phenoxy-propyl-1-yl, phenyl, CH_2-S-Ph, 4-(1,1-Dimethyl-propyl)-phenyl-1-yl, 4-methoxy-benzyl, 2-nitro-benzyl, 4-chloro-phenyl-1-yl, naphthyl, 2-isopropyl-5-methyl-cyclohexyloxymethyl, 4-methoxy-benzyl, 2,3-dichloro-phenyl-1-yl, 1-p-tolyl-cyclopentyl, 6-chloro-pyridin-3-yl, 2,5-dimethyl-phenyl-1-yl, 2-methylsulfanyl-ethyl, 2,6-dichloro-phenyl-1-yl, 1-phenyl-propyl-1-yl, 4-methyl-3-nitro-phenyl-1-yl, 2,3,6-trifluoro-phenyl-1-yl, 3-methyl-butane-1-yl, 4-pentyloxy-phenyl-1-yl, 4-methyl-phenyl-1-yl, 2,4-dimethoxy-phenyl-1-yl, or benzo[1,3]dioxol-5-yl.

The novel process of the present invention is summarized in Scheme-I below.

SCHEME-I



2 3



Formula I

Experimental details of each step of the process are discussed below.

Experimental Details

General Comments

The novel process of the present invention uses reagents and starting materials available from commercial sources including Aldrich Chemicals, Advanced ChemTech, Sigma and the like. Starting materials can also be prepared by methods known to one skilled in the art. Some such methods are discussed below.

Starting Materials

Compounds of Formula 2: General Procedure

Compounds of Formula 2 can be prepared by treating a corresponding benzonitrile with hydroxylamine hydrochloride in the presence of a base with ethanol as the solvent. After stirring the reaction mixture for a few hours, the reaction mixture is concentrated and the resulting residue triturated with water to yield a compound of Formula 2 as a precipitate.

Specific compounds of Formula 2 were prepared by procedures discussed below.

Method A: 4-Methoxybenzamidoxime: A mixture of hydroxylamine hydrochloride (12.0 g 0.172 mol) and DIPEA (22.2 g, 0.172 mol) in ethanol (350 mL) was stirred while 4-methoxybenzonitrile (19.2 g, 0.144 mol) was added. The resulting mixture was stirred at ambient temperature for about 12 to 24 hours and then concentrated in vacuo to yield an oily residue. The oily residue was triturated with water (300 mL) and the resulting precipitate was isolated, washed with H_2O, and dried in vacuo to afford the desired product (17.5 g, 73%) .

MS (ESI) m/z 167 (M+H, 100%)
^{1}H-NMR (DMSO-d_6) δ: 3.75 (s, 3H), 5.75 (s, 2H), 6.90 (d, 2H), 7.65 (d, 2H), 9.45 (s, 1H).

The following compounds of Formula 2 were prepared using the procedure in Method A above.

4-Methylbenzamidoxime

MS (ESI) m/z 150 (100%).

^{1}H-NMR (DMSO-d_6) δ: 2.28 (s, 3H), 5.77 (s, 2H), 7.2 (d, 2H), 7.6 (d, 2H), 9.57 (s, 1H).

Piperonylamidoxime

MS (ESI) m/z 180 (100%)
^{1}H-NMR (DMSO-d_6) δ 5.75 (s, 2H), 6.03 (s, 2H), 6.88 (d, 1H), 7.23 (d, 2H), 9.51 (s, 1H).

3,4-Dimethylbenzamidoxime

MS (ESI) m/z 165 (M+H, 100%)

^{1}H-NMR (DMSO-d_6) δ: 2.23 (s, 6H), 5.75 (s, 2H), 7.2 (d, 1H), 7.36-7.48 (m, 2H), 9.5 (s, 1H).

4-Methylsulfonylbenzamidoxime

MS (ESI) m/z 215 (M+H, 100%)

^{1}H-NMR (DMSO-d_6) δ: 3.23 (s, 3H), 6.0 (s, 2H), 7.87 (s, 4H), 9.98 (s, 1H).

3-Methoxybenzamidoxime

MS (ESI) m/z 167 (M+H, 100%)

^{1}H-NMR (DMSO-d_6) δ: 3.77 (s, 3H), 5.85 (s, 2H), 6.9-7.35 (m, 4H), 9.7 (s, 1H).

3-Methylbenzamidoxime

MS (ESI) m/z 151 (M+H, 100%)

^{1}H-NMR (DMSO-d_6) δ 2.33 (s, 3H), 5.75 (s, 2H), 7.2-7.5 (m, 4H), 9.6 (s, 1H).

4-*n*-Butoxybenzamidoxime

MS (ESI) m/z 209 (M+H, 100%)

^{1}H-NMR (DMSO-d_6) δ: 0.85 (s, 3H), 1.35-1.74 (m, 4H), 3.95 (m, 2H), 5.8 (s, 2H), 6.90 (d, 2H), 7.64 (d, 2H), 9.50 (s, 1H).

Method B: 2-Methoxybenzamidoxime. A suspension of hydroxylamine hydrochloride (11.5 g; 0.165 mol), Na_2CO_3 (17.5 g, 0.165 mol) and 2-methoxybenzonitrile (20.0 g) in a mixture of EtOH (350 mL) and H_2O (30 mL) was heated at 80°C for 10 hours, and the filtered residue washed with EtOH. The combined filtrate was concentrated in vacuo to give a semi solid product which was triturated with a mixture of ether/hexane to yield a white solid, which was isolated and washed with hexane then dried to afford 17.4 g (70%) of the desired product.

MS (ESI) m/z 167 (M+H, 100%)
^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.81 (s, 3H), 5.6 (s, 2H), 6.90 (t, 1H), 7.10 (d, 1H), 7.35 (t, 2H), 9.40 (s, 1H).

Compounds of Formula 3

The other starting material utilized in reaction Scheme I is a protected amino acid represented by a compound of Formula 3. These compounds comprise an amino group and a carboxylic acid group. The amino group is generally protected with a protecting group (e.g., a Boc group). These compounds of Formula 3 can be purchased from commercial sources including Sigma, Nova Biochem and Advanced ChemTech. Specific compounds of Formula 3 were synthesized as outlined by the following procedures.

4-(BOC-aminomethyl)benzoic acid: A solution of NaOH (5.80 g, 0.145 mol) in H_2O (250 mL) was mixed with 4-(aminomethyl)benzoic acid (20.0 g, 0.132 mol) . After the acid had dissolved, a solution of di-*t*-butyl-dicarbonate (31.8 g, 0.145 mol) in THF (100 mL) was added. The mixture was stirred at room temperature for 8-16

hours and then concentrated in vacuo to remove most of the THF. The resulting aqueous layer was acidified to pH 2-3 with solid $KHSO_4$. The mixture was extracted with ether and the combined extracts were dried ($MgSO_4$) and concentrated to yield 32.7 g (99%) of the title compound as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.39 (s, 9H), 4.20 (d, 2H), 7.36 (d, 2H), 7.48 (t, 1H), 7.88 (d, 2H).

BOC-trans-4-(Aminomethyl)cyclohexanecarboxylic acid: This compound was prepared using the general procedure for Boc-protection outlined above

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.75-0.95 (m, 2H), 1.35 (s, 9H), 1.22-1.3 (m, 3H), 1.73 (d, 2H), 1.85 (d, 2H), 2.13 (m, 1H), 2.80 (t, 2H), 6.79 (t, 1H).

BOC-DL-3-Aminocyclohexanecarboxylic acid: This compound was prepared using the general procedure for Boc-protection outlined above.

BOC-4-Aminocyclohexanecarboxylic acid. This compound was prepared using the general procedure for Boc-protection outlined above.

BOC-DL-3-Aminobutyric acid: A solution of NaOH (6.40 g, 0.160 mol) in water (250 mL) was mixed with DL-3-aminobutyric acid (15.0 g, 0.145 mol) and a THF solution of $(BOC)_2O$ (0.160 mol). The resulting mixture was stirred at ambient temperature for 8-16 hours and then concentrated in vacuo to remove most of the THF. The resulting aqueous layer was acidified to pH 2-3 with solid $KHSO_4$. The mixture was extracted with ether and the combined extracts were dried ($MgSO_4$) and concentrated to afford 22.5 g (76%) of the title compound as a white solid.

BOC-DL-β-Aminoisobutyric acid: This compound was prepared using the general procedure for Boc-protection outlined above.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.17 (d, 3H), 0.54 (s, 9H), 1.60-1.70 (m, 1H), 2.02-2.12 (m, 1H), 2.25-2.35 (m, 1H), 6.00 (t, 1H), 11.35 (s,1H)

BOC-DL-3-Amino-3-phenylpropionic acid: This compound was prepared using the general procedure for Boc-protection outlined above.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 0.50 (s, 9H), 1.71-1.80 (m, 2H), 4.05 (t, 1H), 6.35-6.45 (m, 5H), 6.70 (d, 1H), 11.37 (s, 1H).

BOC-DL-Nipecotic acid: This compound was prepared using the procedure outlined for the preparation of Boc-DL-3-Aminobutyric acid above.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.38 (s, 9H), 1.42-1.63 (m, 2H), 1.86-1.91 (m, 2H), 2.24-2.32 (m, 1H), 2.81 (dt, 1H), 3.66 (br d, 1H), 3.89 (br s, 2H), 12.3 (s, 1H).

BOC-4-Piperidinoacetic acid: A suspension of 4-pyridylacetic acid hydrochloride (24.3 g, 0.140 mol) and PtO_2 (2.07 g) in AcOH (150 mL) was hydrogenated at 50 psi. This hydrogenated mixture was filtered and the filtrate was concentrated to yield a colorless semi solid mixture. The semi solid mixture was triturated with diethyl ether (250 mL) to yield a suspension and this suspension was stirred for up to 12 hours leading to the formation of a solid. The resulting solid was isolated, washed with ether and hexane and dried in vacuo to give of 4-piperidineacetic acid hydrochloride (25.4 g, 100%) as a white powder.

A solution of NaOH (12.0 g, 0.300 mol) in water (300 mL) was mixed with 4-piperidineacetic acid hydrochloride from above and the resulting mixture was cooled in an ice water bath. The cooled mixture was treated with THF (100 mL) followed by $(BOC)_2O$ (0.140 mol) in THF. The resulting solution was agitated at ambient temperature for 8-16 hours. The reaction mixture was concentrated under reduced pressure to yield an aqueous solution. The aqueous solution was washed with ether and then acidified to pH 1-2 with 85% H_3PO_4. The acidic solution was extracted with ethyl acetate, the combined ethyl acetate extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to yield the title compound (29.1 g, 86%) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.01 (dq, 2H), 1.37 (s, 9H), 1.60 (br d, 2H), 1.73-1.82 (m, 1H), 2.12 (d, 2H), 2.67 (br s, 2H), 3.88 (br d, 2H), 12.1 (s, 1H).

BOC-DL-3-(3-piperidino)propionic acid. This compound was prepared by the procedure outlined above.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.00-1.44 (m, with s at 1.37 ppm, 13H), 1.52-1.57 (m, 1H), 1.70-1.75 (m, 1H), 2.23 (t, 2H), 2.78 (br t, 2H), 3.68 (br s, 2H), 12.1 (s, 1H).

Compounds of Formula 6a

Compounds of Formula 6a are available from commercial sources including Aldrich Chemicals, Lancaster and Acros. These compounds of Formula 6a can also

be prepared by procedures known to one skilled in the art. For example, acid chlorides represented by compounds of Formula 6a can be prepared by the mixing a carboxylic acid (1 eq.) with oxalyl chloride (1 to 2 eq.) in an inert medium. This resulting mixture was stirred from about 10 minutes to about an hour at a temperature ranging from about 25°C to about the boiling point of the inert solvent. The mixture was then concentrated to yield the corresponding acid chloride, a compound of Formula 6a.

Compounds of Formula 6b

Compounds of Formula 6b, which are isocyanates, are available from commercial sources such as Aldrich chemicals and Lancaster.

Scheme-I General Procedures

STEP-A

The In a reaction vessel was placed an inert solvent mixture of a compound of Formula 3 (1 eq.). This mixture was sequentially treated with an inert solvent (preferably 1,4-dioxane) mixture of a base, preferably 4-DMAP (0.15 to 0.3 eq.), and 0.9 to 1.2 eq. of a dehydrating agent, preferably EDC also in an inert solvent, preferably $CHCl_3$. This resulting mixture was then agitated for up to 30 minutes followed by the addition of 1 eq. of an appropriate hydroxy amidine, a compound of Formula 2, as an inert solvent mixture, preferably as a 1,4-dioxane mixture. This reaction mixture was agitated from about 12 to about 36 hours followed by dilution with about 1 eq. of a base, preferably triethyl amine. This diluted mixture was further agitated from about 5 to about 30 minutes and heated to a temperature of about 80°C to about 110°C in an inert atmosphere for about 4 to about 10 hours.

The workup procedure consists of diluting the reaction mixture with an inert solvent, preferably $CHCl_3$, followed by dilution with an aqueous carboxylic acid solution, a preferred carboxylic acid solution being an aqueous 10% citric acid solution, to form a two phase mixture. This mixture was filtered through a pre-activated hydromatrix material, pre-activated with a 10% aqueous citric acid solution.

The hydromatrix material was rinsed with additional amounts of $CHCl_3$ and the combined filtrate was concentrated to yield a compound of Formula 4.

STEP-B

The compound of Formula 4 is treated with a deprotecting agent (e.g., TFA), optionally in the presence of a cation scavenger (e.g., anisole), and the resulting mixture is agitated from about 1 to about 3 hours. The reaction mixture is then concentrated and the residue is dissolved in a 50% aqueous acetonitrile solution. This solution is maintained at about -80°C for at least about five hours, preferably up to about 18 hours, and then lyophilized to yield a compound of Formula 5.

STEP-C(i)

The compound of Formula 5 is treated with about 2 to about 5 eq. of a base, preferably a solution of DIPEA in $CHCl_3$, followed by the addition of about 0.8 to about 2 eq. of a compound of Formula 6a, i.e., an acid chloride or sulfonyl chloride, which acts as an acylating agent. The compound of Formula 6a preferably is used a solution, typically in an inert solvent and preferably in $CHCl_3$.

The above reaction mixture is agitated at ambient temperature for up to 3 hours. About 1 to about 5 eq. of a 10% aqueous solution of Na_2CO_3 then is added and this resulting mixture is agitated for up to 4 hours. The reaction mixture is then filtered through preactivated hydromatrix material (preactivated with 10% Na_2CO_3). The hydromatrix material is washed with an inert solvent, preferably CH_2Cl_2, and the combined filtrate is diluted with about 1 to about 5 eq. HCl (as a 2N solution). The acidified mixture is agitated for about 1 to about 4 hours and filtered through preactivated hydromatrix material (preactivated with 2N HCl). The hydromatrix material is washed with an inert solvent, preferably CH_2Cl_2, to remove any trapped reaction product. The combined filtrate is passed through silica and evaporated to yield a residue. This residue is lyophilized to yield a compound of Formula I.

STEP-C(ii)

The compound of Formula 5 (1 eq.) is treated with about 1 to about 3 eq. of base, (e.g., DIPEA) in an inert solvent (e.g., ACN, $CHCl_3$ or mixtures thereof). The

mixture is agitated for up to about 30 minutes and then about 0.8 to about 2 eq. of a compound of Formula 6b is added, typically as a solution in an inert solvent, preferably in $CHCl_3$. This resulting mixture is stirred for 12-24 hours and then diluted with a 10% aqueous Na_2CO_3 solution. The solution is mixed and then filtered through pre-activated hydromatrix material (preactivated with 10% aqueous Na_2CO_3 solution). The hydromatrix material is rinsed with $CHCl_3$ and the combined filtrate is treated with 2N aqueous HCl.

The acidified mixture is agitated for about 1 to about 4 hours and filtered through preactivated hydromatrix material (preactivated with 2N HCl). The hydromatrix material is washed with an inert solvent, preferably CH_2Cl_2, to remove any trapped reaction product. The combined filtrate is passed through silica and evaporated to yield a residue. This residue is lyophilized to yield a compound of Formula I.

Library Synthesis

The present process can also be used to prepare an array or a library of compounds. Experimental details to prepare such an array or library are discussed below.

STEP-A

Solutions of compounds of Formula 3 in 1,4-dioxane (700 mL, 0.14 mmol) was dispensed into arranged wells of square well Beckman plate using Robbins Hydra™ 96 well dispenser (Robbins Scientific, catalog number 1029-80-1). Solutions of DMAP in 1,4-dioxane (80 μL, 0.04 mmol) and EDC in $CHCl_3$ (140 μL, 0.14 mmol) were dispensed sequentially to each well. The plates were shaken on microtiter plate shaker (IKA works; VWR Scientific, Catalog No. 33994-228) for 5-10 minutes and then solutions of compounds of Formula 2 in 1,4-dioxane 9700 μL, 0.14 mmol) were dispensed in to assigned wells. The plates were covered with a teflon sheet, clamped and shaken on a reciprocal shaker number 57008-195) at setting 6 for 18 hours. The plates were removed from the shaker and unclamped and then triethyl amine (20 μL, 0.14 mmol) was dispensed into each well. The plates were returned to the reciprocal shake, clamped, and shaken on setting 5 for 4-5 minutes.

The reaction mixtures of each well were concentrated by heating the plate, uncovered, at 100-105°C in a nitrogen-purged oven of 7 hours. The plates were removed from the oven and allowed to cool to room temperature.

The residue in each well was dissolved in $CHCl_3$ (1 mL) and 10% aqueous citric acid solution (300 mL) dispensed in to each well. The plates were shaken on a reciprocal shaker for 2 h. The two-phase mixtures were transferred to Polyfiltronics plates (type PP, 10 μm) with wells previously half-filled with hydromatrix material and pre-activated of 10% aq. citric acid (500 μL) and the plates were placed over 2-mL square-well Beckman collection plates. Each source well is rinsed once with $CHCl_3$ (250 μL) and the rinse transferred to corresponding well of the Polyfiltronics plate. Each well of the Polyfiltronics plate was washed with $CHCl_3$ (2x250 mL) and allowed to drain. The solution in the collection plates was concentrated in a Genevac evaporator for 3-4 h (Atlas, catalog number HT-12-CDOP), to yield a library of compounds of Formula 4.

STEP-B

A 1:1 mixture (v:v) of TFA in DCM (1 mL) was dispensed into each well of the plates obtained from STEP-A. A teflon sheet was secured on top of each plate and was shaken on a reciprocal shaker for 2 hours. The contents of each well were concentrated in a Genevac evaporator for 3-4 hours. The residues in each well were redissolved in 50% aqueous ACN (1 mL) and the plates were shaken on an IKA Works microtiter plate shaker (IKA Works Inc., VWR Scientific, catalog number 33994-220) for 30 minutes. Alternatively the well contents were agitated in parallel using a modified Chiron Mimetopes "PIN" holder fitted with 96 pegs. The solutions then were frozen and stored in a -80°C freezer (Revco, catalog ULT-2586-7 A) for 5-16 hours. The well contents (or solutions) then were lyophilized in a tray lyophilizer (Virtis Unitop, catalog number 800L; tray temperature: 20°C) for 18 hours to yield a library of compounds of Formula 5.

STEP-C(i)

A solution of DIPEA in $CHCl_3$ (500 μL; 0.322 mmol) was dispensed in to each well of the plates obtained from STEP-B and the plates were shaken for 5-10

min. Solutions of compounds of Formula 6a in $CHCl_3$ (840 μL; 0.126 mmol) were added in to each well. The plates were covered with a teflon sheet, clamped, and shaken on a reciprocal shaker for 18 hours.

The plates were removed from the shaker and 10% aqueous Na_2CO_3 solution (300 μL) was dispensed in to each well. The plates were shaken on a reciprocal shaker for 2 hours and the mixtures were transferred to Polyfiltronics plates (PP, 10 μm) with wells previously half-filled with hydromatrix material and pre-activated with 10% aqueous Na_2CO_3 (500 μL). The plates were placed over 2-mL square-well Beckman plates. Each source well is rinsed once with $CHCl_3$ (250 μL) and the rinse was transferred to the corresponding well of the Polyfiltronics plates. Each well of the Polyfiltronics plates was washed with $CHCl_3$ (2 x 250 μL) and allowed to drain into the Beckman plates.

2 N aqueous HCl was dispensed in to each well and the plates were shaken on a reciprocal shaker for 2 hours. The mixtures were filtered through Polyfiltronics plates (PP, 10 μm) with wells previously half-filled with hydromatrix material and pre-activated with 2N HCl (500 μL) in to 2-mL square-well Beckman plates with wells loaded with 100-120 mg of Dowex-1 anion exchange resin. Each source well was rinsed with $CHCl_3$ (2x250 μL) and the rinses drained into Beckman collection plates which in turn were put into a plastic container. The plastic container was tightly-capped and shaken on a reciprocal shaker for 8-16 hours.

The mixtures were transferred, using the Robbins Hydra™ fitted with small gauge needles to prevent clogging by the resin, to Polyfiltronics plates (PP, 10 μm) with wells previously loaded with a thin layer of silica gel (30-40 mg; Baxter Scientific Products, 60Å, 230-400 mesh; catalog number C4582-85) and filtered in to 2-mL Beckman plates. Each well of the reaction plates were rinsed with $CHCl_3$ (2x250 μL) and the rinses transferred to the Polyfiltronics plates. The filtrate in each well of the Beckman plates was concentrated on a Genevac evaporator for 3-4 hours.

ACN (1.25 mL) was dispensed in to each well and the plates were shaken on an orbital shaker for 30 minutes and the solutions were sonicated for 15-20 minutes. The plates were centrifuged for 30 minutes in either the Savant or Genevac evaporators without applying heat or vacuum. The supernatant solutions were

transferred by the Robbins Hydra™ to a set of second pre-weighed 2-mL square-well Beckman plates. The plates were placed in a freezer at -80°C for 5-16 hours and the solutions lyophilized in a tray lyophilizer (tray temperature: 20°C) for 18 hours.

STEP-C(ii)

A 0.4 M solution of DIPEA in $CHCl_3$ (450 μL; 0.182 mmol) was suspended in to each well of the plates obtained in STEP-B and the plates were shaken for 5-10 min. Solutions of compounds of Formula 6b in $CHCl_3$ (840 μL; 0.126 mmol) were dispensed in to each well and the plates were covered with a Teflon sheet, clamped, and shaken on a reciprocal shaker for 18 h.

The plates were removed from the shaker and 10% aqueous Na_2CO_3 solution (300 μL) was added to each well. The plates were shaken on a reciprocal shaker for 2 hours and then the mixtures were filtered through Polyfiltronics plates (PP, 10 μm) with wells previously half-filled with hydromatrix material and pre-activated with 10% aqueous Na_2CO_3 (500 μL) in to 2 mL square-well Beckman plates. Each well is rinsed once with $CHCl_3$ (250 μL) and rinse was transferred in the Polyfiltronics plates was washed with $CHCl_3$ (2x250 μL). The wells of the Polyfiltronics plates were drained into the Beckman plates.

2 N aqueous HCl (300 μL) was dispensed in to each well of the Beckman plates and the plates were shaken on a reciprocal shaker for 2 hours. The contents of each well were filtered through Polyfiltronics plates (PP, 10 μm), comprising wells previously half-filled with hydromatrix material and pre-activated with 2 N HCl (500 μL), in to 2 mL square-well Beckman plates with wells previously loaded with 100-120 mg of Dowex-1 anion exchange resin. Each source well is rinsed with $CHCl_3$ (2x250 μL) and the rinses transferred to the Polyfiltronics plates. The wells of the Polyfiltronics plates were washed through with $CHCl_3$ (250 μL) and allowed to drain in to the Beckman collection plates which were put into a plastic container and shaken on a reciprocal shaker overnight.

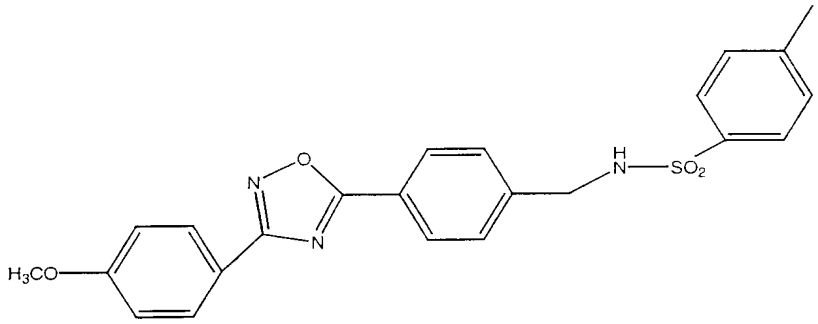
The contents of the wells were filtered through Polyfiltronics plates (PP, 10 μm) with wells previously loaded with a thin layer of silica gel (30-40 mg; Baxter Scientific Products, 60Å, 230-400 mesh; catalog number C4582-85) in to 2 mL

Beckman collection plates. Each well of the reaction plates was rinsed with $CHCl_3$ (2x250 μL) and the rinses transferred to the Polyfiltronics plates. The solvent contents of the wells in the collection plates were concentrated on a Genevac evaporator for 3-4 hours.

ACN (1.25 mL) was dispensed in to each well and the plates were shaken on an orbital shaker for 30 minutes. The mixtures then were sonicated for another 15-20 minutes. The plates were centrifuged for 30 minutes in either the Savant or Genevac evaporators without applying heat or vacuum. The supernatants were transferred by the Robbins Hydra™ to a set of second pre-weighed 2 mL square-well Beckman plates. The plates were placed in the -80°C freezer for 5-16 hours. The mixtures then were lyophilized in a tray lyophilizer (tray temperature: 20°C) for 18 hours.

The following standards were prepared using the novel process of the present invention.

Standard-1

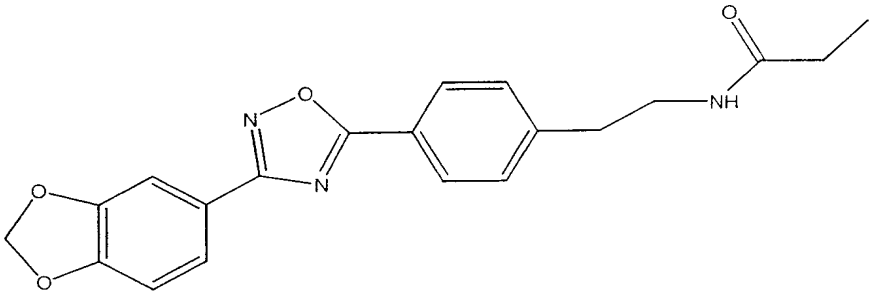


Molecular formula: $C_{23}H_{21}N_3O_4S$

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.87 (s, 3H), 4.23 (d, 2H), 4.78 (t, 1H), 7.00 (d, 2H), 7.30 (d, 2H), 7.38 (d, 2H), 7.75 (d, 2H), 8.11 (m, 4H).

Elemental Analysis:	%C	%H	%N
Calcd:	63.43	4.89	9.65
Found:	63.40	4.96	9.72

Standard-2

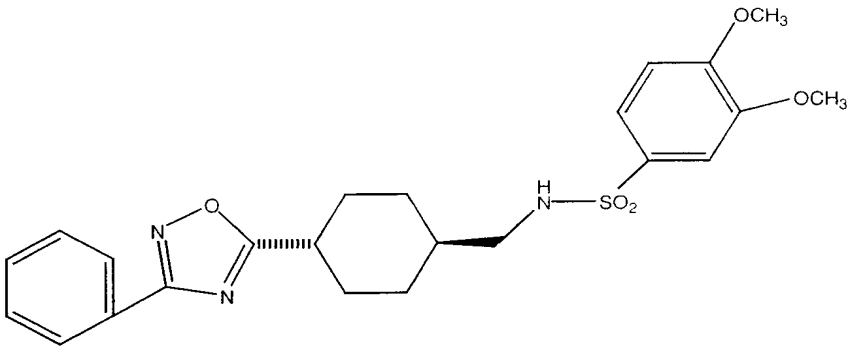


Molecular formula: $C_{14}H_{15}N_3O_4$

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H), 2.21 (q, 2H), 3.23 (t, 2H), 3.76 (q, 2H), 6.05 (s, 2H), 6.15, (br s, 1H), 6.90 (d, 1H), 7.50 (s, 1H), 7.64 (d, 1H).

Elemental Analysis:	%C	%H	%N
Calcd:	58.13	5.23	14.53
Found:	58.29	5.41	14.61

Standard-3

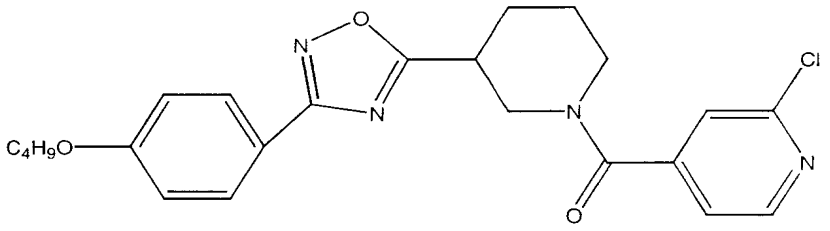


Molecular formula: $C_{23}H_{27}N_3O_5S$

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.09-2.24 (m, 9H), 2.8-2.91 (m, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.50 (br s, 1H), 6.93 (d, 1H), 7.31 (s, 1H), 7.41 (m, 4H), 8.05 (d, 2H).

Elemental Analysis:	%C	%H	%N
Calcd:	60.38	5.95	9.18
Found:	60.33	6.03	9.31

Standard-4



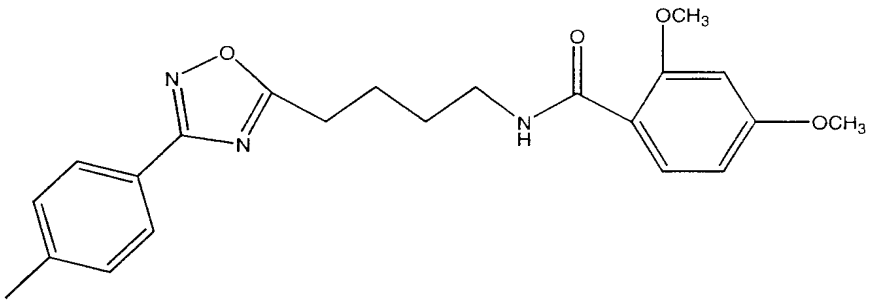
Molecular formula: $C_{23}H_{25}ClN_4O_3$

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.91 (t, 3H), 1.40-2.20 (m, 7H), 2.35 (br s, 1H), 3.15-3.75 (m, 4H), 3.76-4.35 (m, with t at 3.99, 3H), 6.90 (d, 2H), 7.40 (d, 1H), 7.70 (d, 1H), 8.94 (br s, 2H), 8.45 (s, 1H).

Elemental Analysis:	%C	%H	%N
Calcd:	62.65	5.71	12.71
Found:	62.85	5.76	12.74

Standard-5

Structure:

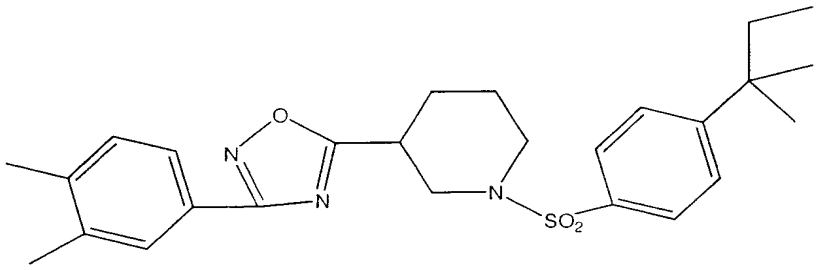


Molecular formula: $C_{22}H_{25}N_3O_4$

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.72 (m, 2H), 1.95 (m, 2H), 2.38 (s, 3H), 2.97 (t, 2H), 3.49 (q, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 6.44 (d, 1H), 6.59 (q, 1H), 7.25 (d, 2H), 7.77 (br s, 1H), 7.9 (d, 2H), 8.14 (d, 1H).

Elemental Analysis:	%C	%H	%N
Calcd:	66.82	6.37	10.63
Found:	66.93	6.42	10.52

Standard-6

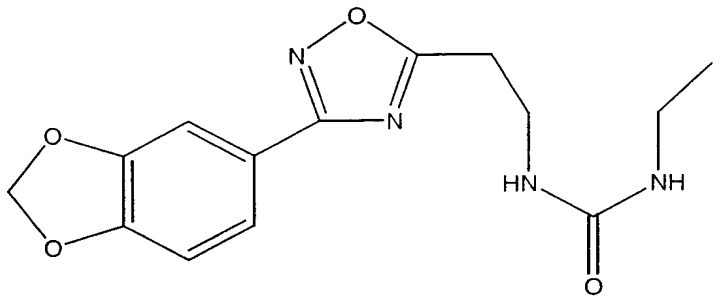


Molecular formula: $C_{26}H_{33}N_3O_3S$

^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.67 (t, 3H), 1.29 (s, 6H), 1.61-1.70 (m, 4H), 2.20-2.45 (m, with s at 2.32, 9H), 2.69 (t, 1H), 3.28-3.39 (m, 1H), 3.81 (br d, 1H), 4.15 (br d, 1H), 7.26 (d, 1H), 7.51 (d, 2H), 7.71 (d, 2H), 7.75-7.82, (m, 2H).

Elemental Analysis:	%C	%H	%N
Calcd:	66.78	7.11	8.99
Found:	66.59	7.11	8.70

Standard-7



Molecular formula: $C_{14}H_{16}N_4O_4$

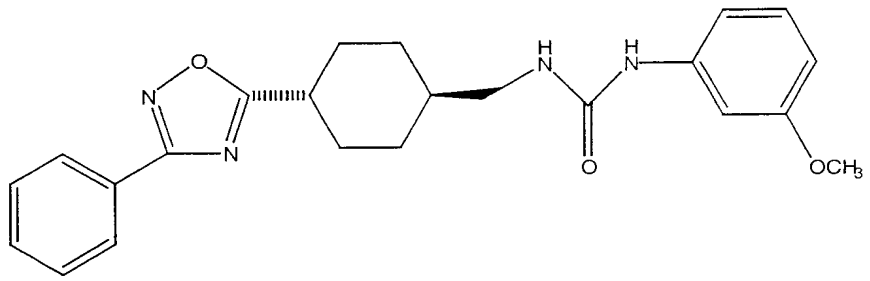
^{1}H-NMR (300 MHz, CD_3OD) δ: 1.06 (t, 3H), 3.05-3.25 (m, with t at 3.11, 4H), 3.30 (s, 1H), 3.59 (t, 3H), 4.89 (s, 2H), 6.04 (s, 2H), 6.94 (d, 1H), 7.47 (s, 1H), 7.62 (d, 1H)

^{13}C-NMR (270 MHz, $CD_3OD/CDCl_3$) δ: 14.6, 27.5, 34.7, 36.8, 101.7, 108.4, 122.0, 148.1, 150.3, 159.3, 167.9, 178.5

MS m/z 305 (M+H, 100%).

Elemental Analysis:	%C	%H	%N
Calcd:	55.26	5.30	18.41
Found:	55.50	5.46	18.60

Standard-8



Molecular formula: $C_{23}H_{26}N_4O_3$

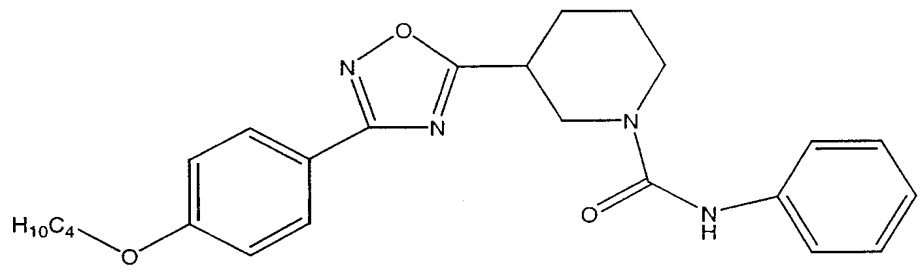
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.00-1.10 (m, 2H), 1.49-1.70 (m, 4H), 1.85-1.90 (m, 2H), 2.15-2.21 (m, 2H), 3.90 (br t, 1H), 3.12 (t, 2H), 3.74 (s, 3H), 5.71 (t, 1H), 6.70 (d, 1H), 6.85 (d, 1H), 7.03 (s, 1H), 7.17 (t, 1H), 7.45 (d, 2H), 7.57 (s, 1H), 8.05 (d, 2H)

^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 29.8, 36.5, 37.6, 46.0, 55.2, 106.3, 108.7, 112.5, 127.4, 128.9, 130.0, 131.1, 140.3, 156.6, 160.4, 168.2, 182.6

MS m/z 407 (M+H, 100%).

Elemental Analysis:	%C	%H	%N
Calcd:	67.96	6.45	13.78
Found:	67.73	6.29	13.75

Standard-9



Molecular formula: $C_{24}H_{28}N_4O_3$

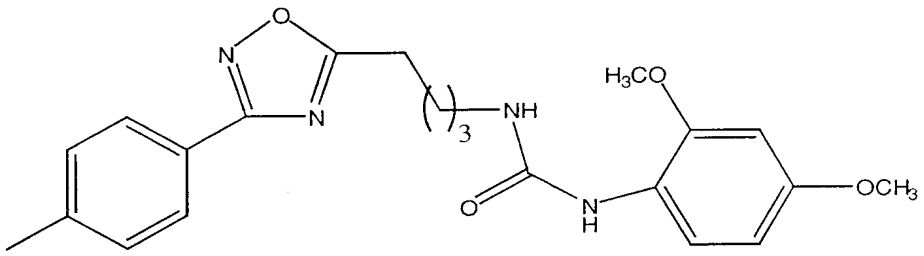
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (t, 3H), 1.40-1.95 (m, 7H), 2.10-2.20 (m, 2H), 3.23-2.26 (m, 1H), 3.45-3.50 (m, 1H), 3.52-3.61 (m, 1H), 3.90-4.04 (m, 4H), 6.95 (d, 2H), 7.20-7.42 (m, 5H), 7.96 (d, 2H)

^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 13.9, 19.3, 23.5, 27.9, 31.3, 34.5, 44.4, 47.7, 67.9, 114.8, 118.6, 119.8, 122.9, 128.9, 129.2, 139.4, 155.3, 161.7, 168.0, 179.8

MS m/z 421 (M+H, 100%).

Elemental Analysis:	%C	%H	%N
Calcd:	68.55	6.71	13.32
Found:	68.38	6.73	13.29

Standard-10



Molecular formula: $C_{22}H_{26}N_4O_4$

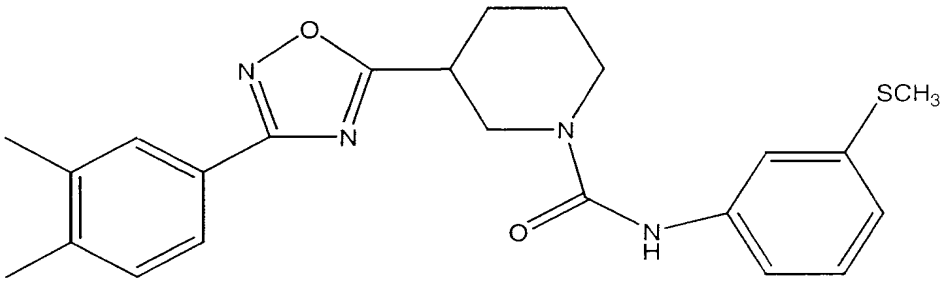
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.60-1.65 (m, 2H), 1.92-1.97 (m, 2H), 2.42 (s, 3H), 2.98 (t, 2H), 2.40 (q, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 4.66 (br t, 1H), 6.30 (s, 1H), 6.47 (d, 2H), 7.30 (d, 2H), 7.65 (d, 1H), 7.94 (d, 1H)

^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 21.6, 23.9, 26.3, 29.6, 39.7, 55.6, 55.7, 99.1, 104.1, 121.2, 122.8, 124.0, 127.3, 129.6, 141.5, 151.1, 156.4, 156.8, 168.3, 179.5

MS m/z 411 (M+H, 100%).

Elemental Analysis:	%C	%H	%N
Calcd:	64.37	6.38	13.65
Found:	64.12	6.48	13.43

Standard-11



Molecular formula: $C_{23}H_{26}N_4O_2S$

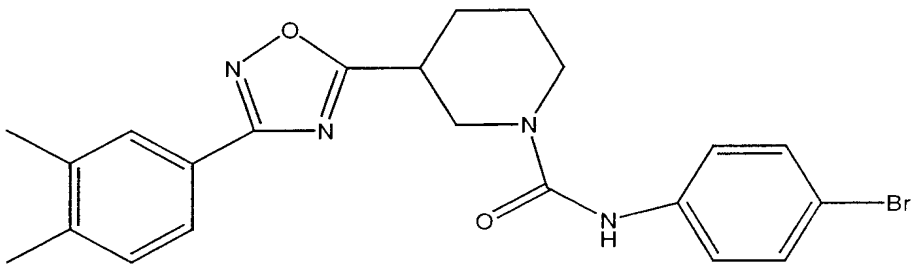
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55-1.70 (m, 4H), 2.10-2.30 (m, 3H), 2.28 (s, 3H), 2.33 (s, 3H), 2.43 (s, 3H), 3.20-3.27 (m, 2H), 3.75-3.90 (m, 2H), 4.07-4.15 (dd, 1H), 6.90 (d, 1H), 7.07 (d, 1H), 7.15 (t, 1H), 7.23 (d, 1H), 7.35 (s, 1H), 7.52 (s, 1H), 7.78 (d, 1H)

^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 15.7, 19.7, 20.0, 23.4, 27.8, 34.4, 44.3, 47.8, 116.4, 117.4, 120.9, 123.9, 125.0, 128.6, 129.1, 130.3, 137.5, 139.3, 140.0, 140.6, 155.4, 168.4, 179.9

MS m/z 423 (M+H, 100%).

Elemental Analysis:	%C	%H	%C
Calcd:	65.38	6.20	13.26
Found:	65.18	6.16	13.08

Standard-12



Molecular formula: $C_{22}H_{23}BrN_4O_2$

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55-1.75 (m, 4H), 2.11-2.28 (m, 3H), 2.24 (s, 3H), 2.30 (s, 3H), 3.25-3.40 (m, 2H), 3.80-3.90 (m, 2H), 4.10-4.15 (dd, 1H), 7.25 (d, 2H), 7.37 (d, 2H), 7.60 (s, 1H), 7.78 (d, 2H)

^{13}C-NMR (67.5 MHz, $CDCl_3$) δ: 19.7, 20.0, 23.3, 27.6, 34.4, 44.2, 47.9, 115.1, 121.2, 123.8, 125.1, 128.5, 130.3, 131.8, 137.5, 138.7, 140.7, 155.2, 168.3, 179.9

MS: m/z 455 (M+H, 100%).

Elemental Analysis:	%C	%H	%N
Calcd:	58.03	5.09	12.30
Found:	57.98	5.30	12.36

Analysis Procedure

A. Chromatography: All standards were analyzed on a Hewlett Packard HP1100 HPLC employing a Zorbax 4.6 mm x 7.5 cm SP-C18 column with a guard column. Standards were monitored at UV settings of 214 and 254 nm. The column was heated at 40°C and the flow rate was 0.800 mL per minute for all runs. Gradient elution was performed using water with 0.05% TFA (solvent A) and acetonitrile containing 0.05% TFA (solvent B) as mobile phases. Most samples were prepared as dilute solutions in acetonitrile, methanol or mixtures thereof.

HPLC Gradient:

Time (minutes)	% Solvent B
0.00	0.00
5.00	100
8.00	100.0
9.50	0.00

B. Mass Spectrometry: Identity of peaks observed by HPLC were determined by electrospray (ESI) LC/MS analysis on a Finnigan TSQ 7000 mass spectrometer with a Hewlett Packard HP1050 HPLC. Alternatively, purified compounds or relatively pure mixtures were analyzed with a Hewlett Packard 5989 particle beam mass spectrometer and Hewlett Packard 59980 LC/MS interface in either CI or EI mode, with a Hewlett Packard HP1050 HPLC using methanol as mobile phase for direct injection of samples. Most samples were prepared as dilute solutions in acetonitrile or methanol. For analysis of both the test library and production library, direct injection

MS analysis was performed on the Sciex 150 MCA, Shimadzu LC-10 HPLC, according to the following conditions:

LC/MS Assay:

Mobile A:	Water (containing 0.05% AcOH and 1.0% MeOH)
Mobile B:	Methanol (containing 0.05% AcOH and 1.0% water)
Flow Rate:	0.3 mL/min
Sample volume:	10.0 μL
Column:	Zorbax 3.0 x 50.0 mm column with inline filter
Temp.:	40 °C
Gradient:	0 to 100% B in 6.0 min, 100% B for 1.0 min, 0% B for 2.0 min.
Detection:	UV monitoring at 214, 254, 280, and 320 nm

MS Assay:

Mode: Positive ion ESI injection volume 5 □L flow rate 0.3 mL/min, 50% solvent B.

DEFINITIONS

Alkyl: "Alkyl", or "alkyl radical" is meant to indicate a hydrocarbon moiety of up to 14 carbon atoms, unless indicated otherwise. This hydrocarbon is generally attached to at least one other atom, and can be straight chain, or branched, or cyclic, or a combination thereof. The term "straight chain alkyl" is meant to represent an unbranched hydrocarbon moiety of up to 8 carbon atoms. An example of a straight chain alkyl is a n-pentyl group.

Alkelene: The term "alkelene" represents an alkyl group, as defined above, except that it has at least one center of unsaturation, i.e., a double bond. Illustrative examples are butene, propene, and pentene.

Alkylene: The term "alkylene" represents a straight chain, branched, cyclic or a combination thereof hydrocarbon group which is attached to two other groups. Examples are $-CH_2-$ (methylene), cyclohexylene and $-CH_2-CH_2-$ (ethylene).

Array of compounds: This term indicates a collection of independent (individual) compounds that are synthesized by the process of the present invention. Generally the term array of compounds indicates a collection of individual compounds distinct from one another. Also included in the array (library) of compounds is a mixture of the individual compounds. The term "library of compounds" can be interchangeably used with the term 'array of compounds".

Aryl: The terms "Ar" and "aryl", as used herein, are intended to represent a stable substituted or unsubstituted (collectively also referred to as 'optionally substituted') six to fourteen membered mono-, bi- or tri-cyclic hydrocarbon radical comprising carbon and hydrogen atoms. Illustrative examples are phenyl (Ph), naphthyl, anthracyl groups, and piperanyl. The aryl group preferably is substituted with one to three substituents selected from H, C_{1-8} straight chain or branched alkyl, OC_{1-4} alkyl, halogen and SC_{1-4} alkyl.

Heteroaryl: The term "heteroaryl" is intended to represent a stable 5 to 10 membered aryl group ("aryl" as defined above), wherein one or more of the carbon atoms is replaced by a hetero atom selected from N, O, and S. The hetero atoms can exist in their chemically allowed oxidation states. Thus a Sulfur (S) atom can exist as a sulfide, sulfoxide, or sulfone. Preferred heteroaryl groups are six membered ring systems comprising not more than 2 hetero atoms. Illustrative examples of preferred heteroaryl groups are thienyl, N-substituted succinimide, 3-(alkyl amino)-5,5-dialkyl-2-cyclohexen-1-one, methyl pyridyl, alkyl theophylline, furyl, pyrrolyl, indolyl, pyrimidinyl, isoxazolyl, purinyl, imidazolyl, pyridyl, pyrazolyl, quinolyl, and pyrazinyl. A hetero aryl group is preferably substituted with one to three substituents selected from H, C_{1-8} straight chain or branched alkyl, OC_{1-4} alkyl, halogen and SC_{1-4} alkyl.

Catalyst: The term "catalyst " is intended to represent an additive that facilitates the course of a reaction but does not get incorporated in to the final product. Illustrative examples of catalysts are N-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt) and N-hydroxysuccinimide. The term solid support (SS), as used in the present invention, signifies polymeric material for supported synthesis. A detailed description of the terms linker molecule, and solid support can be found in

The Combinatorial Index, B. A. Bunin, 1998, which is incorporated herein by reference.

Cation Scavenger: The term "cation scavenger" as used herein represents a reagent which can intercept a cation generated during a reaction, for example under acidic conditions. By intercepting the cation the cation scavenger can prevent the cation from reacting with the product formed during the reaction. Illustrative examples of cation scavengers are water, triethylsilane, anisole, thioanisole, dimethylsulfide, phenol and 1,2-ethanedithiol.

Optional or Optionally: The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally is substituted with one to three substituents" means that the group referred to may or may not be substituted in order to fall within the scope of the invention. Thus the term "optionally substituted" is intended to mean that any one or more hydrogens on a designated atom can be replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. When the substituent is keto (=O) then 2 hydrogens on the atom are replaced.

Inert Solvent: The term "inert solvent" is intended to represent solvents which do not react with the reagents dissolved therein. Illustrative examples of inert solvents are tetrahydrofuran (THF), methylene chloride, dichloro methane (DCM), ethyl acetate (EtOAc), dimethyl formamide (DMF), diaoxane, chloroform, and DMSO.

Protecting Group (PG): "Protecting group" or "PG", as used in the present invention, is a group that is attached to, or placed on, an atom so the protected atom does not react with reactants , thereby temporarily rendering the protected atom inactive. Illustrative examples of protecting groups are tetrahydropyran (THP), tert-butyl-oxy carbonyl (BOC), and fluoromethyloxy carbonyl (FMOC). A comprehensive list and description of protecting groups can be found in Protective groups in Organic Synthesis, second edition, T.W. Greene and P.G.M. Wuts, 1991, which are incorporated herein by reference.

Deprotecting Agent: The term "deprotecting agent" is used to mean an agent which

selectively removes a PG from a functional group such as an amine group. The deprotecting agent can be an acidic or basic moiety as understood by one skilled in the art. The term "protecting group" or "PG", as used herein, indicates a group that protects an amine functional group rendering the amine inactive. A detailed description of the terms "deprotecting agent", and "protecting group" (PG) is available in Protective Groups in Organic Synthesis, 2nd edition, T. W. Greene and P. G. M. Wuts, 1991, which is incorporated herein by reference.

Dehydrating Agent: As used herein the term "dehydrating agent" (also some times referred to as "drying agent") represents an agent which facilitates removal of any water or moisture which may be present in a reaction mixture or formed during a reaction. Typical dehydrating/drying agents known to one skilled in the art are intended to be included herein. Representative examples of dehydrating/drying agents are magnesium sulfate, sodium sulfate, trimethyl orthoformate, triethyl orthoformate, trimethyl ortho acetate and triethyl ortho acetate. or any moisture which may be present in

Base (as used in step (C)): The term "suitable base" as used in step (C) herein represents an amino compound which can absorb or abstract a proton from a compound of Formula 5. A desirable class of the suitable base is tertiary amines. Illustrative examples of the suitable base are N-methylmorpholine (NMM), N-ethylmorpholine, N-methylpiperidine, N-ethylpiperidine, triethyl amine, pyridine, lutidine and N,N-diisopropylethylamine (DIPEA), alkali metal salts of trimethyl silanol, potassium trimethylsilanoate, tetrabutylammonium hydroxide, tetramethylammonium hydroxide, lithium hydroxide and aqueous solutions of alkali metal hydroxides, carbonates and bicarbonates..

As used in the present invention, the illustration:

generally indicates a point of attachment of the group, comprising the illustration, to another group or atom.

Halogen: The term "halo" or "halogen" is intended to represent Cl, Br, I and F.

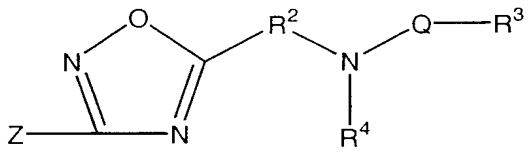
Abbreviations:

ACD = Available Chemicals Directory

ACN = Acetonitrile
AcOH = Acetic Acid
AUC = Area under curve
BAM = Benzamidoxime
BOC = t-Butoxycarbonyl
CI = Chemical Ionization
CDI = 1,1'-Carbonyldiimidazole
1,2-DCE = 1,2-Dichloroethane
DCM = Dichloromethane
DIPEA = N,N-Diisopropylethylamine
DIC = 1,3-Diisopropylcarbodiimide
DMAP = 4-(Dimethylamino)pyridine
EDC = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI = Electron Impact
ESI = Electrospray ionization
HCl = Hydrochloric Acid
HOBt = 1-Hydroxybenzotriazole
HPLC = High Performance Liquid Chromatography
LLE = Liquid Liquid Extraction

CLAIMS

1. A process for synthesizing a compound or an array of compounds of Formula I



.....Formula I

wherein:

Z represents an aryl group substituted with R^1, R^5 and R^6;

Q represents CO, SO_2 or C(O)NH;

R^2 represents C_1-C_{14} alkylene, C_1-C_{14} substituted alkylene, $(CH_2)_{0-6}$-Ar, Ar-$(CH_2)_{1-6}$, or C_{5-10} cycloalkylene-$(CH_2)_{0-6}$;

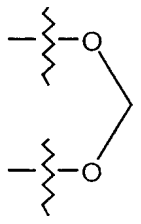
R^3 represents C_1-C_{14} alkyl, aryl, substituted aryl, C_1-C_{14} alkylene-aryl, C_1-C_{10} alkylene-O-aryl, C_1-C_{10} alkylene-S-aryl, heteroaryl or C_1-C_{10} alkylene-S-C_1-C_6 alkyl;

R^4 represents H or C_{1-4} alkyl;

alternatively R^2 and R^4 along with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclic ring substituted with at least one substituent selected from C_{1-4} alkyl, Ph, OH, H, OC_{1-4} alkyl, NHCO-C_{1-4} alkyl and halogen; and

R^1, R^5 and R^6 independently at each occurance are selected from H, C_{1-6} alkyl, O-C_{1-6} alkyl and SO_2-C_{1-4} alkyl;

alternatively, when on adjacent carbon atoms, R^5 and R^6 can be taken together to form



;

said process comprising

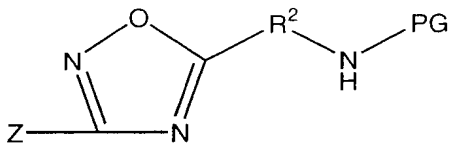
(A) treating a compound of Formula 2

$$Z\text{-}C(=NOH)NH_2 \qquad \text{.....Formula 2}$$

with a compound of Formula 3

$$HOOC\text{-}R^2\text{-}NH\text{-}PG \qquad \text{.....Formula 3}$$

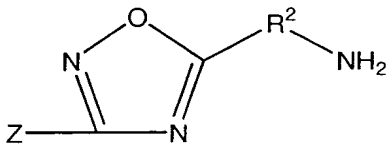
in the presence of a dehydrating agent and optionally in the presence of a catalyst, at a temperature of from about 25°C to about 85°C,
to yield a compound of Formula 4



.....Formula 4

where Z and R^2 are as defined above, and PG represents a protecting group;

(B) treating a compound of Formula 4 with a deprotecting agent, optionally in the presence of a cation scavenger, to yield a compound of Formula 5



.....Formula 5

where Z and R^2 are as defined above;

(C) treating a compound of Formula 5 with:

(i) a compound of Formula 6a

R^3-Q-X .....Formula 6a

in the presence of a base, and where R^3 is as defined above, Q represents CO or SO_2, and X represents a halogen, to yield a compound of Formula I, or

(ii) a compound of Formula 6b

R^3-N=C=O .....Formula 6b

in the presence of a base, and where R^3 is as defined above, to yield a compound of Formula I, wherein Q represents C(O)-NH.

2. A process of Claim 1 wherein the dehydrating agent in step (A) is selected from EDC, DIC, DCC and CDI.

3. A process of claim 2 wherein step (A) is carried out in the presence of a catalyst selected from DBU, Et_3N, 4-DMAP and HOBt.

4. A process of claim 3 wherein the deprotecting agent in step (B) is selected from HCl, HBr, HF, hydrochromic acid, *p*-toluene sulfonic acid, formic acid and TFA.

5. A process of claim 4 wherein the cation scavenger in step (B) is anisole.

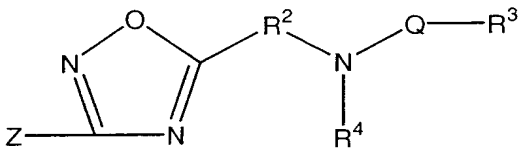
6. A process of Claim 5 wherein the base in step (C) is selected from N-methyl morpholine, triethyl amine, pyridine, N,N-diisopropyl ethyl amine, N-methyl piperidine, N-ethyl morpholine and 2,6-lutidine.

7. A process of claim 6 wherein Z represents a phenyl group substituted with R^1, R^5 and R^6.

8. A process of claim 7 wherein R^1, R^5 and R^6 are independently selected from H, CH_3, C_2H_5, OCH_3, OC_2H_5 and SO_2CH_3.

9. A process of claim 8 wherein R^3 represents 2,3,5,6-tetramethyl-phenyl, 3,4-dimethoxy-phenyl, 2-ethoxy-phen-1-yl, 4-isopropyl-phen-1-yl, 2-Ethoxy-naphthalen-1-yl, 1-phenoxy-propyl-1-yl, phenyl, CH_2-S-Ph, 4-(1,1-Dimethyl-propyl)-phenyl-1-yl, 4-methoxy-benzyl, 2-nitro-benzyl, 4-chloro-phenyl-1-yl, naphthyl, 2-isopropyl-5-methyl-cyclohexyloxymethyl, 4-methoxy-benzyl, 2,3-dichloro-phenyl-1-yl, 1-p-tolyl-cyclopentyl, 6-chloro-pyridin-3-yl, 2,5-dimethyl-phenyl-1-yl, 2-methylsulfanyl-ethyl, 2,6-dichloro-phenyl-1-yl, 1-phenyl-propyl-1-yl, 4-methyl-3-nitro-phenyl-1-yl, 2,3,6-trifluoro-phenyl-1-yl, 3-methyl-butane-1-yl, 4-pentyloxy-phenyl-1-yl, 4-methyl-phenyl-1-yl, 2,4-dimethoxy-phenyl-1-yl, or benzo[1,3]dioxol-5-yl.

10. An array of compounds of Formula I



.....Formula I

wherein:

Z represents an aryl group substituted with R^1, R^5 and R^6;

Q represents CO, SO_2 or C(O)NH;

R^2 represents C_1-C_{14} alkylene, C_1-C_{14} substituted alkylene, $(CH_2)_{0-6}$-Ar, Ar-$(CH_2)_{0-6}$, or C_{5-10} cycloalkylene-$(CH_2)_{0-6}$;

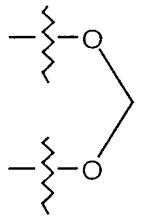
R^3 represents C_1-C_{14} alkyl, aryl, substituted aryl, C_1-C_{14} alkylene-aryl, C_1-C_{10} alkylene-O-aryl, C_1-C_{10} alkylene-S-aryl, heteroaryl, or C_1-C_{10} alkylene-S-C_1-C_6 alkyl;

R^4 represents H or C_{1-4} alkyl;

alternatively R^2 and R^4 along with the nitrogen atom to which they are attached form a 4 to 7 membered heterocyclic ring substituted with at least one substituent selected from C_{1-4} alkyl, Ph, OH, H, OC_{1-4} alkyl, NHCO-C_{1-4} alkyl and halogen; and

R^1, R^5 and R^6 independently at each occurance are selected from H, C_{1-6} alkyl, O-C_{1-6} alkyl and SO_2-C_{1-4} alkyl;

alternatively when on adjacent carbon atoms, R^5 and R^6 can be taken together to form



11. The array of compounds of claim 10 wherein

R^1, R^5 and R^6 are independently selected from H, CH_3, C_2H_5, OCH_3, OC_2H_5 and SO_2CH_3; and

R^3 represents 2,3,5,6-tetramethyl-phenyl, 3,4-dimethoxy-phenyl, 2-ethoxy-phen-1-yl, 4-isopropyl-phen-1-yl, 2-Ethoxy-naphthalen-1-yl, 1-phenoxy-propyl-1-yl, phenyl, CH_2-S-Ph, 4-(1,1-Dimethyl-propyl)-phenyl-1-yl, 4-methoxy-benzyl, 2-nitro-benzyl, 4-chloro-phenyl-1-yl, naphthyl, 2-isopropyl-5-methyl-cyclohexyloxymethyl, 4-methoxy-benzyl, 2,3-dichloro-phenyl-1-yl, 1-p-tolyl-cyclopentyl, 6-chloro-pyridin-3-yl, 2,5-dimethyl-phenyl-1-yl, 2-methylsulfanyl-ethyl, 2,6-dichloro-phenyl-1-yl, 1-phenyl-propyl-1-yl, 4-methyl-3-nitro-phenyl-1-yl, 2,3,6-trifluoro-phenyl-1-yl, 3-methyl-butane-1-yl, 4-pentyloxy-phenyl-1-yl, 4-methyl-phenyl-1-yl, 2,4-dimethoxy-phenyl-1-yl, or benzo[1,3]dioxol-5-yl.

INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/US 00/17577

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D271/06 C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MOUSSEBOIS C ET AL: "Synthèse de deux nouveaux acides amines phénoliques comportant un cycle 1,2,4-oxadiazole" HELVETICA CHIMICA ACTA, vol. 60, no. 1, 26 January 1977 (1977-01-26), pages 237-42, XP002148163 the whole document ---	1-9
Y	BORG S ET AL: "1,2,4-Oxadiazole derivatives of phenylalanine: potential inhibitors of substance P endopeptidase" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 10, 1993, pages 801-10, XP002148164 the whole document ---	1-9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 September 2000	11/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Allard, M

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/US 00/17577

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	NAGAHARA K ET AL: "Sur la formation d'oxadiazoles-1,2,4 par action de benzamidoximes sur des anhydrides isatoïques" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 23, no. 12, December 1975 (1975-12), pages 3178-83, XP002148162 the whole document	1-9
A	page 3179, compounds 23-25	10,11
A	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerdering der Chemischen Wissenschaften; XP002148165 Beilstein Registry Number 749142 & GAZZ. CHIM. ITAL., vol. 93, 1963, pages 1196-1205,	10,11
A	CORSARO A ET AL: "Activation of nitriles by hydrogen bonding in cycloadditions with nitrile oxides" JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 21, 1984, pages 949-52, XP002148161 the whole document	1,10,11
P,X	WO 00 25768 A (TREGA BIOSCIENCES, INC) 11 May 2000 (2000-05-11) the whole document	1-11

3

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic Application No
PCT/US 00/17577

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0025768 A	11-05-2000	AU 1455500 A	22-05-2000